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Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma

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Summary

Melanoma is the most common lethal cutaneous neoplasm. In order to harmonise treatment and follow-up of melanoma patients, guidelines for the management of melanoma in Switzerland were inaugurated in 2001 and revised in 2006. A new classification and recent results in randomised trials necessitated changes concerning staging and modifications of the recommendations of therapy and follow-up.

Key words: melanoma; guidelines; staging; therapy; follow-up

Introduction

Cutaneous melanoma not only has a high incidence, but is also the most aggressive of the cutaneous neoplasms. For these reasons, treatment guidelines have been prepared under the aegis of the Swiss Cancer League (skin cancer group) and published in 2001 with a revised version in 2006 [1], with the aim of providing a reasonably practical guide for all physicians (general practitioners, dermatologists, surgeons, oncologists, and others) who encounter cutaneous melanoma in their daily work. The recommendations presented in these guidelines have been graded according to the amount of scientific evidence supporting them using the “Level of Evidence” classification developed by the Canadian Medical Association, 1998.

The purpose of these updated guidelines is to ensure the adequate treatment of melanoma patients in Switzerland. At present, patients with low risk melanoma tend to be over-treated, whereas the follow-up procedures for patients with high risk or metastasing melanoma are sometimes inadequate. These guidelines were introduced in April 1999 in the Departments of Dermatology in Geneva and Lausanne/Switzerland and Zurich/Switzerland, and have been in use since that time. Our experience with the guidelines showed them to provide a valuable, practical basis for treating cutaneous melanoma. Drawing on the combined expertise of a multidisciplinary team, the guidelines reflect current international standards [2] and the state of the art. Modifica-

tions of these guidelines in special clinical situations are at the discretion of the individual practitioner.

There are several important differences between the Swiss recommendation and other recommendations:

1. The ABCD-rule does not contain diameter because today many melanomas have diameter of less than 5 mm.
2. Based on daily experience the quality of the sentinel lymph node procedure (surgery and histological evaluation of the node) is sometimes poor in Switzerland. The guidelines therefore underline the necessity of sending patients with intermediate risk to specialised centers in order to assure reasonable quality.
3. The best population for an adjuvant interferon therapy are patients with micrometastases and/or ulceration. Pegylated interferon-alpha 2b weekly injected is preferred based on its favourable pharmacology.
4. Compared to standard therapy, new molecules such as ipilimumab and vemurafenib are promising treatment options. In order to improve our knowledge about the optimal use, translational research is essential. This can only be done in specialised centers, therefore we recommend that these patients are referred to and treated in melanoma centers.
5. PET/CT scans are covered by the Swiss health insurances for melanoma follow up and should be preferentially used in the early periods in high risk situations.

Medical progress and new information necessitated an update of these recommendations in 2011.

Clinical melanoma subtypes

Superficial spreading melanoma (SSM) is the most common subtype (70%) and is characterised by an initial flat phase that shows changes in size, shape or colour. SSM may occur in young adults but the mean age is in the 40s. Large numbers of melanocytic naevi and more than a few dysplastic naevi are strong risk factors. SSM is associated

with and has been linked to intermittent exposure and sun-burn especially in adolescence and childhood.

Nodular melanoma (NM) accounts for about 15% of melanomas overall, except for the majority of thick melanomas. It presents as a symmetrical, raised, firm, often uniformly coloured and frequently non-pigmented nodule that is rapidly enlarging and becoming more raised. Bleeding and crusting are common. NM occurs more often in older people, particularly men, and is more commonly seen on the head and neck than elsewhere.

Lentigo maligna (LM) and lentigo maligna melanoma (LMM, the invasive form of LM) account for 10–15% of melanomas. It has an initial flat phase that may be prolonged. It presents as an evolving pigmented macule and has to be differentiated from seborrheic keratoses, solar lentigines and pigmented actinic keratoses. LM has been linked epidemiologically to large cumulative doses of UV light, has a strong predilection for the head and neck, and is more common in outdoor workers, in older people and in association with solar damage and non-melanoma skin cancer.

Acral lentiginous melanoma (ALM) accounts for 1–3% of melanomas and occurs on the acral skin of the palms and soles. It presents with a flat phase with similar appearances and changes to SSM. Importantly, melanomas that appear relatively flat on the soles of the feet may have significant depth histologically. Although the epidemiology is not as well understood, this type of melanoma is at least equally common in people with dark skin and may have no relationship with UV exposure.

Rare variants of melanoma

There are some rare variants of melanoma such as melanoma of the nail matrix (subungual melanoma), of the mucosa (e.g., oral cavity, esophagus, rectum, vagina) amelanotic melanoma, desmoplastic melanoma which represent together not more than 5% of all melanomas.

Diagnosis of melanoma

Examination for melanoma detection requires examination of the whole skin surface under good lighting. Dermoscopy is a non invasive technique using a hand-held magnifying device combined with either the application of a liquid between the transparent plate of the device and the skin, or the use of cross-polarised light. This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye and has been shown to significantly improve diagnostic accuracy compared to naked eye examination in the hands of an experienced investigator (level of evidence III).

Suspicious lesions are characterised by **A**symmetry, **B**order irregularities, **C**olor heterogeneity, **D**ynamics, (Dynamics in colors, elevation or size) (“ABCD rule”) [2, 3]. Dynamics is the most important criterium for the diagnosis of thick melanomas including amelanotic melanoma. Today, many primary melanomas have a diameter of less than 5 mm [4]. Diagnosis should be based on a full thickness excisional biopsy with a small side margin. Processing by an experienced pathology institute is mandatory.

Staging

Physical examination with special attention to other suspicious pigmented lesions, tumour satellites, in-transit metastases, regional lymph node and systemic metastases is mandatory.

In low-risk melanomas (tumour thickness <1 mm) no other investigations are necessary. In higher stages imaging is recommended in order to allow proper staging.

The most recent version of the AJCC classification has made a few changes. Mitotic activity was included as a criterion for thin primary tumours. In addition, the assumption was made that even solitary tumour cells should result in N1a disease. The clinical relevance of this suggestion is under discussion.

The refined version of the pTNM [5] system (table 1) is the classification system of choice.

Therapy

Primary excision of suspicious lesions

Diagnosis should be based on a full thickness excisional biopsy. Suspicious melanocytic lesions should be excised completely, with a narrow clinical margin (level of evidence IV). The diagnosis of melanoma is made histologically. The histology report should follow the WHO classification and include maximum thickness in millimeters (Breslow), presence of ulceration and mitosis, presence and extent of regression and clearance of the surgical margins [6].

The final operative removal of the primary tumor should be carried out within 4 to 6 weeks following primary resection, leaving a safety margin of 1–2 cm, depending on the thickness of the tumor (table 2). Special localisations, e.g. in the face, may necessitate exceptions from standard safety margins. In these locations, radiotherapy might be considered as an alternative for lentigo maligna (melanoma) [7].

Sentinel lymph node biopsy

In the past decade, sentinel lymph node biopsy (SLNB) has become standard for staging patients diagnosed with cutaneous melanoma. The method's accuracy and reliability and the status of the sentinel lymph node (SLN) as the single most important prognostic factor for recurrence and survival for melanoma patients has been proven beyond any reasonable doubt (level of evidence IV) [8]. Nevertheless, the impact of sentinel lymph node biopsy (SLNB) on survival remains unclear. There is general agreement that SLNB will help identify patients who might benefit from further therapy, such as complete lymph node dissection (CLND) and adjuvant interferon therapy [9, 10], even if clinical trials aiming to determine the impact of these adjuvant measures are still ongoing. The recently published proceedings of an expert panel clarify the indication of SLNB as a staging tool [8]: SLNB should be discussed with and offered to all patients with primary melanoma with Breslow thickness equal to or greater than 1.0 mm and clinically normal regional lymph nodes (determined by physical examination and ultrasound).

According the current TNM classification (UICC International Union Against Cancer, Issue 7) micro metastases

have to be distinguished from isolated tumour cells. Isolated tumour cells are single tumour cells or small clusters of cells, that are smaller than 0.2 mm and can be detected by immunohistochemistry and are also visible in conventional stainings. Isolated tumour cells do not have typical features of metastases such as proliferation or stroma reactions and do not penetrate and do not show vasculature.

The pathology report of the sentinel lymph node-biopsy should clearly distinguish between isolated tumour cells and tumour cell clusters. In the case of micrometastases it is essential to indicate the maximal diameter of the lymph node metastasis. In order to provide high quality of histopathological assessments the histological diagnosis of melanoma should be confirmed by a referenced pathologist for quality reassurance [11].

The pathological investigation of the sentinel lymph node is difficult and should be performed in pathology institutes with large amounts of experience.

Completion lymph node dissection

In the pre-sentinel era, melanoma patients were subject to elective lymph node dissections (ELND), which, however, did not produce a statistically significant survival benefit [12]. Following the introduction of SLNB as standard of care in the treatment regime of cutaneous melanoma, complete lymph node dissection (CLND) was recommended according to the Augsburg Consensus guidelines [13] to

all patients with a positive SLNB. Thus, roughly 80% of all patients, who were sentinel-negative, were spared elective lymph node dissection. Whereas SLNB is a minimally invasive procedure with limited morbidity, CLND, much like ELND, is associated with considerable complication rates and socioeconomic costs [14]. Several studies report an increased disease-free survival (DFS) with no significant impact on overall survival, raising the question whether lymph node dissection is necessary in case of a positive SLNB. In a recent study, CLND reduced subsequent regional lymph node metastases and improved disease-free survival, while overall survival remained unaffected [15]. 67–90% of SLN-positive patients do not have further non-SLNs that contain tumour deposits in the CLND specimens [16]. As a consequence, the majority (80%) of SLN-positive patients undergo unnecessary surgery associated with considerable morbidity. Therefore, several authors have tried to identify patient, tumour and SLN characteristics predicting further non-SLN positivity to safely avoid CLND [16]. Although previous studies have failed to consistently identify the same clinicopathological features as indicators for additional non-SLN positivity upon CLND or for DFS [17], SLN tumour load, nevertheless, was uniformly confirmed by all of these studies as prognosticator for non-SLN positivity and recurrence. CLND has not yet been proven to improve overall melanoma-specific survival. However, Cascinelli et al. [18] have shown that CLND

Table 1: The 2009 staging system for cutaneous melanoma according to the AJCC [5].

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤1.00	a: Without ulceration and mitoses <1/mm ² b: With ulceration or mitoses ≥1/mm ²
T2	1.01–2.00	a: Without ulceration b: With ulceration
T3	2.01–4.00	a: Without ulceration b: With ulceration
T4	>4.00	a: Without ulceration b: With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2–3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
 *Micrometastases are diagnosed after sentinel lymph node biopsy.
 †Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically

Table 2: Excision safety margins for surgical treatment of primary melanoma (pT1–4N0M0).

Tumour thickness (Breslow)	Excision safety margin, cm
Melanoma in situ (tumour thickness is not indicated) (pIisN0M0)	0.5
<2 mm (pT1–2N0M0)	1
>2 mm (pT3–4N0M0)	2

is necessary to achieve the best assessment of prognosis of stage IB and II melanoma and to identify those patients who, having only positive sentinel nodes and negative non-sentinel nodes, have a good prognosis. There is considerable debate as to how to stratify SLN tumour burden; Satzger et al. [19] found that isolated immunohistochemically positive tumour cells are without prognostic significance and DFS of these patients did not differ from that of SLN-negative patients, an observation that is supported in a broader sense by Van Akkooi et al. [20]. In their study, no patient with an SLN tumour load of <0.1 mm had additional non-SLN positivity upon CLND, and 5-year overall survival was 100%.

On the basis of these data, they suggested that such patients may be considered SLN-negative and should be spared CLND. There is currently no consensus among eminent guidelines [8, 9] whether or not CLND should be recommended for all patients with positive SLNB. Therefore, we do not recommend CLND complete lymph node dissection in patients that present only isolated tumour cells in their sentinel node until the presence of this pathological feature has shown clear prognostic implications. Discrepancies exist in particular as far as the role of the SLN tumour burden is concerned and on the value of ultrasound-guided follow-up, a method that can detect early recurrences in the regional nodal basin and prompt a CLND only in patients with such evidence. Based on these differing expert opinions, the benefits and shortcomings of CLND should be discussed with each patient with a positive SLNB carefully, until the currently ongoing Multicenter Selective Lymphadenectomy Trial II has clarified these issues. Recurrences in the regional nodal basin, irrespective of whether it was previously staged or not, mandate lymph node dissection [21]. However, before undertaking additional aggressive local surgical treatments, a detailed staging investigation, one including imaging techniques such as CT scan or PET (positron emission tomography), is necessary to exclude the presence of further metastases.

Adjuvant therapy

Many clinical trials have investigated the impact of adjuvant treatment modalities in high risk melanoma. However, solid evidence can only be gleaned from prospective randomised multicenter trials. Neither ELND, perfusion of the extremities, radiotherapy, nor chemotherapy have been able to identify a significant increase in the length of survival rate benefit to the melanoma patient collective as a whole [2]. Adjuvant treatment with viscum album (Iscador®) is not recommended, since it might accelerate the disease course [22]. Therefore, there is no generally accepted adjuvant therapy to date for patients with high-risk primary melanoma or completely resected lymph node metastases (stage III). Adjuvant immunotherapy with interferon- α leads to a significant prolongation of disease-free survival in some, but not all randomised trials. Several large independent trials using intermediate dose (also pegylated interferon) have demonstrated a positive effect on disease free and distant metastases-free survival in patients with micro metastases (N1a) [10]. In this patient population and patients with primary ulcerated melanomas interferon can be recommended, if the individual patient

tolerates it well (level of evidence III). Adjuvant treatment in patients with resected macroscopic involvement (N1b) should only be applied in the context of clinical trials in specialised centers.

Surgery of distant metastasis

The purpose of treatment in the metastatic situation is usually to achieve a palliation. Surgery is the most effective means of providing this, if it is technically feasible, if risk of morbidity and mortality is low and if the patient is likely to live long enough to derive a benefit. A PET CT scan should be performed before surgery to exclude further lesions. Good examples for palliative surgery are single localised lesions to the brain, bowel, liver and lung or spinal cord. In some patients a long time survival after complete resection has been described [23].

Radiotherapy

Radiotherapy plays an important role in the palliation of many symptoms in melanoma patients especially for symptomatic brain metastases or localised and painful bone metastases, as well as nerve compression symptoms. A short course of radiotherapy is normally preferred and good palliation can be obtained in two thirds of the cases. The overall response rate reported with different fractional doses ranges from 9–92% with a median of 50% [24–26]. Radiotherapy still represents a reasonable palliation whenever surgery is not applicable (table 3).

Systemic treatment of metastatic melanoma

Patients should be included in well-designed clinical trials whenever possible after genetic analysis of c-kit, N-Ras and B-RAF. Unfortunately clinical trials are not available for all melanoma patients. In these cases and in B-RAF and c-kit wildtype patients, systemic treatment with Ipilimumab or monotherapy should be considered. Dacarbazine (DTIC) is one of the most used substances in metastatic melanoma and is still the reference treatment in many countries. Temozolomide demonstrated efficacy equal to that of DTIC in two phase III trials [27, 28]. No difference in overall survival, progression free survival and overall response rate was seen between the two arms. One advantage of temozolomide is the better penetration into the central nervous system. Several case reports have shown a regression of CNS metastases under treatment with temozolomide. Treatment with bisphosphonates should be considered in patients with bone metastases. In aggressive symptomatic disease, a polychemotherapy containing cisplatin, vindesine and dacarbazine in first line (response rate: 40%) [29] or the combination of carboplatin and paclitaxel in second line [30] has produced a partial response in 11% and a disease stabilisation in 51% of the patients. However, an impact on disease free or overall survival was not shown in either study.

Biochemotherapy, a combination of IL-2 and/or interferon alpha with chemotherapeutic agents such as DTIC, temozolomide, fotemustine, cisplatin, carboplatin, vinblastine, paclitaxel or docetaxel has demonstrated a higher response rate but this was not translated into a better survival rate than that with a single agent and has been associated with an increase in toxicity [31, 32] and is not recommended.

There are no randomised clinical trials for IL-2 monotherapy. Some centers still use this therapy in well-selected patients with low tumor burden, despite the lack of convincing phase III data.

The anti-CTLA4 antibody Ipilimumab has very recently been shown to prolong overall survival in 1st and 2nd line therapy of stage IV [33, 34]. Despite the considerable side effects, this treatment option may be considered as 1st or 2nd line therapy. This treatment should only be applied in specialised centers that offer translational research programme to contribute to a better definition of the patient subpopulation that profits from this therapy.

A number of new drugs targeting several pathways have been tested in phase III and failed to show a survival benefit [30]. The selective B-Raf inhibitor vemurafenib (PLX4032) has been investigated in phase II and III studies for patients with B-Raf mutations (50% of melanoma patients) with positive impact on response rate and survival [35]. In patients with symptomatic melanoma (B-Raf mutated) metastases (pain, B symptoms, bulky disease) vemurafenib is considered to be the appropriate first line therapy.

Other molecules, as anti VEGF antibodies have shown promising activity in phase II trials [36, 37]. To conclude, all stage IV melanoma patients need to be referred to reference centers, discussed in an interdisciplinary melanoma tumour board at centers with broad experience in the management of this disease and should be treated preferably in well-designed clinical trials.

Follow-up

The patient should be instructed in avoidance of sunburn, extended unprotected solar or artificial ultraviolet exposure and in lifelong regular self-examination of the skin and

peripheral lymph nodes. The patient must be aware that his family members have an increased melanoma risk.

The aim of melanoma follow up is to detect a relapse or an additional skin tumour as early as possible. The risk of developing a second melanoma is 5–8% within the first 2 years after diagnosis [38]. 35% of patients with lentigo maligna melanoma develop another malignant tumour of the skin during the next 5 years [7]. Although the hypothesis suggesting that regular monitoring reveals early detection of metastasis may be well founded, no randomised studies have demonstrated early detection of metastases improves over all survival [39].

Follow up schedule is based mainly on dated literature and historical practice [40] (level of evidence IV). Despite numerous attempts to achieve international consensus on follow up guidelines there is no universal valid agreement. However, loco regional lymph node metastases are the most common event in patients which are regularly checked. Therefore, it is worthwhile to focus on cutaneous relapses and loco regional lymph nodes. Physical examination remains the mainstay of follow up visits. Besides that, patients should be trained on self examination because most relapses have been detected by themselves. This fact raises the question whether routinely performed clinical examinations and imaging procedures, based on the relapse risk over time, generate a real benefit for melanoma patients [2]. Probably false positive results could be reduced by increasing the time between visits and would be anyhow sufficient for psychological support [2].

While the first 5 years after diagnosis are most important, as 90% of all metastases occur during this period, clinical examinations and imaging procedures have to be more frequent for the first 5 years. Because melanoma is a tumour that could have late metastasis, a lifelong surveillance beyond 10 years is generally recommended [41]. Thin melano-

Table 3	
Number and localisation of the metastases	Treatment modalities 1 st choice 2 nd choice 3 rd choice
In-transit metastases (few) (pTXN2cM0)	1. Surgical removal 2. Radiotherapy
In-transit metastases (multiple, >5) (pTXN2cM0)	1. Perfusion of the extremity ¹ 2. Radiotherapy 3. Chemo-/ targeted / immuno-therapy ¹
Locoregional lymph nodes (pTxN1a,2a)	1. Consider trial participation 2. Additional Interferon alpha treatment ¹
Locoregional lymph nodes (pTxN2b,2c,3)	1. Radical lymphadenectomy, in case of incomplete resection: Radiotherapy 2. Consider trial participation
Solitary central nervous system metastases (pTxNxM3)	1. Neurosurgical removal 2. Stereotactic irradiation ¹ (according to localisation this could also be the 1 st choice)
Solitary lung metastases (pTxNxM1)	1. Surgical removal 2. Consider clinical trial participation 3. Chemo-/ targeted / immuno-therapy ¹
Multiple metastases (pTxNxM1a-1c)	1. Consider clinical trial participation 2. Chemo-/ targeted / immuno-therapy ¹
Painful bone metastases (pTxNxM1a-1c)	1. Consider clinical trial participation 2. Bone specific therapy (e.g., bisphosphonates, denosumab) 3. Consider surgical removal if single lesion, 4. Radiotherapy 5. Chemo-/ targeted / immuno-therapy ¹

¹ These therapies should be restricted to controlled studies at specialised centers.

mas with a Breslow depth less than 1mm have only a small risk of relapse and thus need no imaging. While sonography is easy to perform, cheap, not harmful and more sensitive than clinical examination in revealing lymph node metastasis it should be routinely done. Table 4 presents the suggested time schedule of examinations in Switzerland. To detect further metastasis in stage III (and in stage IIC because of similar prognosis) an imaging study of the whole body, preferably with PET-CT, is recommended [42]. S-100 protein is a good marker for melanoma relapse, especially for disease free survival in stage III melanomas [43, 44]. In stage IV melanomas control intervals have to be individually adjusted according the therapeutical intentions.

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Table 4

Stage (TNM)	Physical examination years 1–3	Physical examination years 4–5	Physical examination years 6–10	Loco regional lymph node sonography years 1–5	S-100 years 1–5	Abdominal sonography and chest X-ray years 1–5	CT, MRI, PET or PET-CT years 1–5
I (≤T1N0)	6	12	12	–	–	–	–
I (T2N0), IIA+B	3	6	6–12	6–12	6–12	individual	–
IIC, III	3	3	6	6	6	individual	6–12
IV	individual	individual	individual	individual	individual	individual	individual

- 80-1 randomised phase iii trial: Rfn-alpha 2b versus rfn-gamma versus iscador m versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. *Eur J Cancer*. 2004;40:390–402.
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